Complete Summary

GUIDELINE TITLE

Primary treatment for locally advanced cervical cancer: concurrent platinum-based chemotherapy and radiation.

BIBLIOGRAPHIC SOURCE(S)

Gynecology Cancer Disease Site Group. Lukka H, Hirte H, Fyles A, Thomas G, Fung Kee Fung M, Johnston M. Primary treatment for locally advanced cervical cancer: concurrent platinum-based chemotherapy and radiation [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jun [online update]. 27 p. (Practice guideline report; no. 4-5). [26 references]

GUIDELINE STATUS

This is the current release of the guideline.

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Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Cervical cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Obstetrics and Gynecology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate whether the addition of concurrent platinum-based chemotherapy improves survival and quality of life with acceptable toxicity for women with cervical cancer in whom radiotherapy is considered appropriate

TARGET POPULATION

Women with cervical cancer for whom primary treatment with radiotherapy is being considered:

- Those with locally advanced cervical cancer
- Those with bulky clinical stage IB (>4 cm) cervical cancer, who are treated with radiotherapy
- Those with high-risk early-stage cervical cancer (node-positive or margin-positive), who will be treated with radiotherapy following hysterectomy

INTERVENTIONS AND PRACTICES CONSIDERED

Primary treatment of locally advanced cervical cancer with:

1. Radiotherapy (pelvic radiotherapy or pelvic + para-aortic radiotherapy) alone
2. Radiotherapy + cisplatin (weekly or twice weekly)
3. Radiotherapy + cisplatin/bleomycin/vincristine
4. Radiotherapy + cisplatin/5-fluorouracil
5. Radiotherapy + hydroxyurea
6. Radiotherapy + cisplatin + hysterectomy
7. Radiotherapy + hysterectomy
8. Hysterectomy + pelvic lymphadenectomy + radiotherapy + cisplatin/5-fluorouracil
9. Hysterectomy + pelvic lymphadenectomy + radiotherapy

MAJOR OUTCOMES CONSIDERED

- Disease-free survival
- Disease recurrence
- Quality of life
- Toxicity

- Survival

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The MEDLINE database was searched from 1966 to March 2002 using the strategy described in Appendix 1 of the original guideline document. The same search strategy was used to find additional citations in the CANCERLIT (1975 to October 2001) and HealthStar (1975 to January 2002) databases. The Cochrane Library (Issue 1, 2002) was also searched for randomized trials and systematic reviews. The reference lists of papers and review articles identified by these sources were scanned as a source of additional citations. The Physician Data Query (PDQ) clinical trial database on the Internet (www.cancer.gov/search/clinical_trials) was searched for reports of ongoing randomized trials. All searches were restricted to English-language publications. The proceedings of the 1999, 2000 and 2001 American Society of Clinical Oncology (ASCO) meetings were scanned for abstracts reporting recent clinical trial results. The Canadian Medical Association (CMA) Infobase (www.cma.ca), the National Guideline Clearinghouse (www.guideline.gov) and other Web sites were searched for existing evidence-based practice guidelines.

2004 Update

The original literature search has been updated using MEDLINE (through June 2004), EMBASE (through week 25 2004), CANCERLIT (through October 2002), the Cochrane Library (Issue 2, 2004), and the 2002-2004 proceedings of the annual meeting of the American Society of Clinical Oncology.

Inclusion Criteria

Articles were selected for inclusion in this practice guideline report if they met all of the following criteria:

1. Reported results of randomized controlled trials (RCTs) or meta-analyses comparing concurrent platinum-based chemotherapy plus radiotherapy with radiotherapy alone or radiotherapy plus non-platinum-based chemotherapy
2. Included patients with cervical cancer (please see Appendix 2 of the original guideline document for staging information)
3. Reported data on survival for each intervention group

Clinical trial results reported in either full papers or abstracts were eligible. Clinical practice guidelines from other guideline-development groups were also eligible for inclusion.

Exclusion Criteria

1. Because resources were not available for translation, non-English-language publications were excluded.
2. Trials of platinum-based neoadjuvant chemotherapy were not included because the mechanism of action of concurrent platinum and radiotherapy (possibly additive effect) is likely different from a neoadjuvant chemotherapy approach (of debulking).

NUMBER OF SOURCE DOCUMENTS

Nine reports of randomized trials (8 randomized trials) of concurrent cisplatin-based chemoradiotherapy met the eligibility criteria. (Note: One of the reports was in abstract form.)

2004 Update

Since the completion of the guideline, the randomized trial that was originally presented in abstract form had been published in full. Another article reporting long term follow-up results from a previously reported trial has also been published. Finally, one new randomized controlled trial (RCT) comparing cisplatin and radiation therapy to radiation therapy alone has been published.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Two of the authors independently reviewed the eligible papers and extracted data regarding the number of patients randomized, disease stage, type of systemic therapy, radiation dose and fractionation, nature of the control group, median follow-up time, completeness of follow-up and numbers of deaths in each group. Disagreements were resolved by consensus. In addition to the information presented in a meeting abstract, data from the National Cancer Institute of Canada's Clinical Trials Group (NCIC CTG) trial was obtained from the investigators (personal communication).

To estimate the overall effect on survival of the addition of chemotherapy, mortality data (the number of patients who had died by the end of the study and the number of patients included in the survival analysis by the investigators) were

abstracted from the published reports of individual randomized controlled trials (RCTs) and pooled using the Review Manager software (RevMan 4.1) provided by the Cochrane Collaboration (Metaview© Update Software). Combining data in this manner assumes a constant hazard ratio of risks for the groups being compared. Results are expressed as relative risks (also known as risk ratios) with 95% confidence intervals (CI), where a relative risk (RR) for mortality less than one indicates that the experimental treatment (platinum-based chemotherapy plus radiotherapy) improved survival compared with the control treatment. Conversely, a relative risk greater than one suggests that patients in the control group experienced lower mortality. The relative risk is calculated by taking the ratio of the proportion of patients who have died in the experimental treatment group to the proportion of patients who have died in the control group. The random-effects model was used for pooling across studies in preference to the fixed-effects model, as the more conservative estimate of effect.

Six sets of studies were identified for subgroup analyses:

1. Those that enrolled women with locally advanced disease
2. Those that enrolled women with high-risk early-stage (stages IB and IIA) disease
3. Those that administered radiotherapy alone in the control group
4. Those where hydroxyurea was added to radiotherapy in the control group
5. Those where cisplatin was given as a single agent with radiotherapy
6. Those where cisplatin plus 5-fluorouracil was used with radiotherapy

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Disease Site Group Consensus Process

The Gynecology Disease Site Group (DSG) reviewed the evidence from seven randomized trials that addressed the role of radiotherapy plus cisplatin-based chemotherapy in various stages of cervical cancer. Meta-analysis of survival data from published reports of these trials detected a significant effect for cisplatin-based chemoradiation compared with control (radiotherapy alone or radiotherapy plus hydroxyurea). The DSG members in attendance concluded that:

- There is a moderate but statistically significant effect on survival of adding concurrent cisplatin-based chemotherapy to radiotherapy in the treatment of locally advanced cervical cancer.
- There is insufficient evidence available to support the addition of 5-fluorouracil to cisplatin.

When the systematic review was incorporated into a draft guideline report, there was debate about the importance of evidence from the Canadian National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) study in the context of the other evidence available from individual trials and from the meta-analysis. The

Canadian trial was not large but was considered to be the 'cleanest' study in that it compared cisplatin as a single agent plus radiotherapy to radiotherapy alone and the radiotherapy was given according to current practice in Ontario. There was concern that the radiotherapy regimens used in some of the other studies may have been inadequate. The DSG decided to base its recommendations on their meta-analysis but acknowledged that there may be differences in approaches to radiotherapy between non-Canadian and Canadian practitioners. Because of the variable quality of the radiotherapy regimens used in the trials and the potential impact on study results, the evidence from other trials may not be generalizable to the Canadian setting.

After reviewing all of the evidence, the DSG recommends that women with cervical cancer for whom primary treatment with radiotherapy is being considered should be offered concurrent cisplatin with their course of radiotherapy.

The DSG discussed the optimal dose of cisplatin. No evidence was available from direct comparisons of different doses of cisplatin and it is possible that doses lower than those used in the randomized controlled trials may be effective. The DSG recommends that cisplatin be given at the dose used in the randomized controlled trials that found a benefit for cisplatin (i.e., 40 mg/m^2). Based on a review of the toxicity data from the randomized controlled trials, the DSG recommends that cisplatin be given weekly.

The definition of the target population for the guideline was reviewed and refined to make it clearer, especially for stage IB disease. Unfortunately, survival data from the subgroup of women with stage IB cervical cancer who participated in the randomized controlled trials in locally advance disease were not available.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 105 practitioners in Ontario (41 medical oncologists, 20 radiation oncologists, 20 surgeons, 2 hematologists, 4 pathologists, and 18 gynecologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package

mailed again). The Gynecology Disease Site Group (DSG) reviewed the results of the survey. Fifty-three responses were received out of the 105 surveys sent (49.5% response rate).

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. All eleven members of the PGCC returned ballots and approved the guideline as written.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Women with cervical cancer for whom treatment with radiotherapy is being considered should be offered concurrent cisplatin with their course of radiotherapy. These women include:
    - Those with locally advanced cervical cancer
    - Those with bulky clinical stage IB (>4 cm) cervical cancer, who are treated with radiotherapy
    - Those with high-risk early-stage cervical cancer (node-positive or margin-positive), who will be treated with radiotherapy following hysterectomy
- There are no direct comparisons of different cisplatin regimens. Based on the review of the available toxicity data from the randomized controlled trials, the Disease Site Group felt that cisplatin should be given weekly (40 mg/m^2).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Increased understanding of the efficacy of cisplatin-based chemotherapy plus radiotherapy as a treatment option for women with cervical cancer in whom radiotherapy is considered appropriate

POTENTIAL HARMS

Rates of serious hematologic, gastrointestinal, and genitourinary acute adverse effects are higher with cisplatin-based chemotherapy plus radiotherapy than with radiotherapy alone.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Despite this recommendation (i.e., that cisplatin be given weekly at 40 mg/m^2), other schedules and doses have been used; thus, there is no conclusive evidence that one dose and schedule is better than the other. See the "Major Recommendations" field.
- There is insufficient evidence available to make recommendations on the addition of 5-fluorouracil (5-FU) to cisplatin during radiotherapy.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgement in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Aug 26 (revised 2004 Jun)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Gynecology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Gynecology Disease Site Group (DSG) disclosed potential conflict of interest information.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Primary treatment for locally advanced cervical cancer: concurrent platinum-based chemotherapy and radiation. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on March 20, 2003. The information was verified by the guideline developer on May 8, 2003. This summary was updated by ECRI on January 23, 2004, and again on September 27, 2004. The updated information was verified by the guideline developer on October 20, 2004.

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Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 9/25/2006